Synthesis S. M. Patel et al. Paper

Copper-Catalyzed Intramolecular α-C–H Amination via Ring-Opening Cyclization Strategy to Quinazolin-4-ones: Development and Application in Rutaecarpine Synthesis

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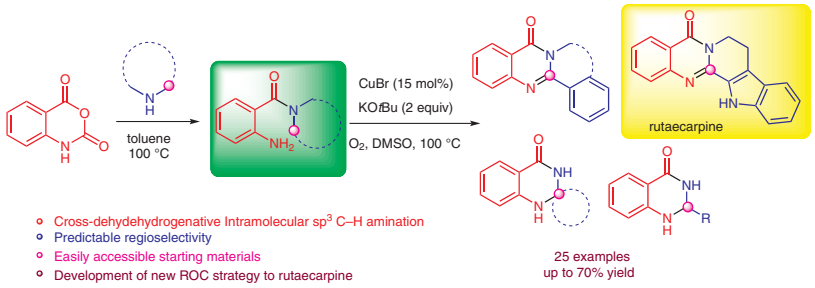


Received: 05.01.2019
Accepted after revision: 19.03.2019
Published online: 15.04.2019
DOI: 10.1055/s-0037-1611575; Art ID: ss-2019-z0004-op

Abstract A copper-catalyzed intramolecular α-C–H amination has been developed for the synthesis of quinazolin-4(3*H*)-one derivatives from commercially available isatoic anhydride and primary and secondary benzylamines via ring-opening cyclization (ROC). This method shows good functional group tolerance and allows access to a range of 2-aryl, 2-alkyl, and spiroquinazolinone derivatives. However, 2-methylquinazolin-4(3*H*)-one was synthesized from 2-amino-*N*-isopropylbenzamide by C–C bond cleavage, and *N*-benzyl-2-(methylamino)benzamide afforded 1-methyl-2-phenylquinazolin-4(1*H*)-one along with 2-phenylquinazolin-4(3*H*)-one by N–C bond cleavage for aromatization. It is the first general method to construct the potentially useful 2-methylquinazolin-4(3*H*)-one by copper-catalyzed intramolecular C–H amination. Also this ROC strategy has been successfully applied to the synthesis of quinazolinone alkaloid rutaecarpine.

Key words intramolecular C-H amination, ring-opening cyclization, rutaecarpine, quinazolin-4(3*H*)-one, 2-methylquinazolin-4(3*H*)-one

Quinazolinone is an important N-heterocyclic scaffold, as seen by their abundance in biologically active compounds and numerous natural products such as rutaecarpine,[1] tryptanthrin,[2] luotonin A, B, E, and F,[3] and bioactive compounds (Figure 1). Owing to the promising biological and medicinal activities including anticancer,[4] anti-inflammatory,[5] antibacterial,[6] and antihypertensive[7] properties, synthetic quinazolinone scaffolds have been highly in demand and remains a challenge in organic synthesis. The direct functionalization of C–H bonds of organic compounds has recently emerged as a diverse atom economic carbon–heteroatom (C–X)[8] and carbon–carbon (C–C) bond formation.[9] Several diverse C–H functionalization methodologies without prefunctionalization of the coupling partners have been widely developed in the past decades.[10] Previously, we have employed N-incorporation strategy for the synthesis of quinoxalines via dual C(sp^2)–H functionalization[11a] and also, in recent past reported on the direct cycloaminative approach to imidazole derivatives via dual C–H functionalization.[11b]

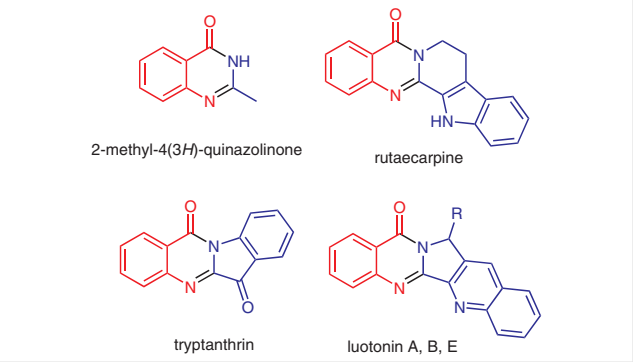
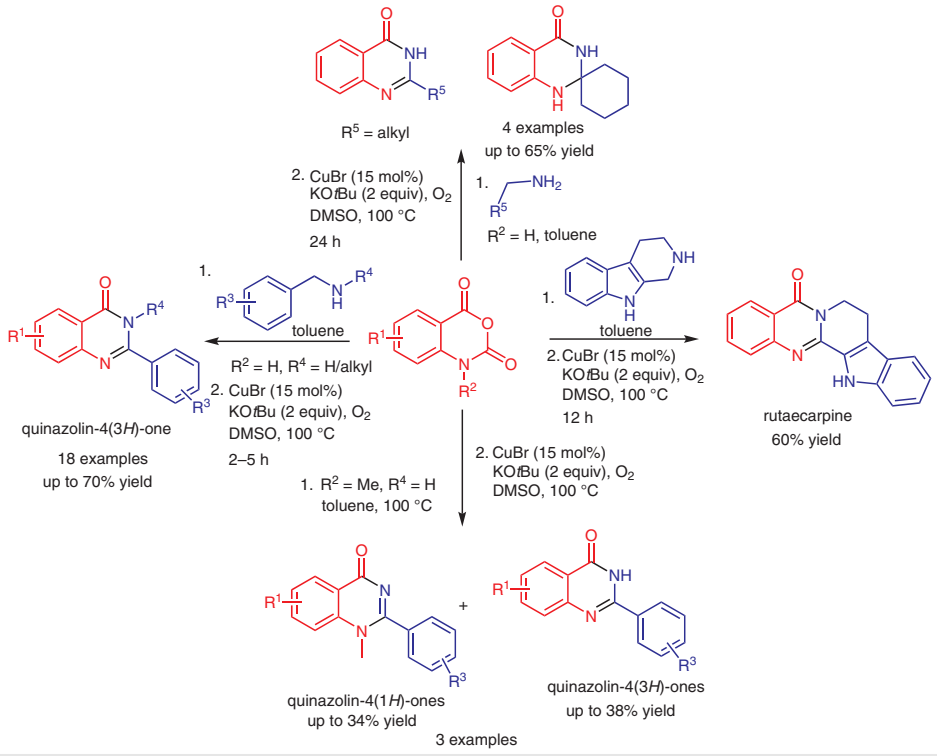


Figure 1 Quinazolinone skeleton containing natural products

Over the past three decades, considerable progress has been made in the development of methods to construct sp^2 carbon–nitrogen (C–N) bonds using palladium, copper, or nickel catalysis. However, formation of sp^3 C–N bonds remains one of the major challenges in the field of cross-coupling chemistry. Recently, much attention has been focused towards the development of transition-metal-catalyzed intramolecular C–H amination strategies to assemble N-heterocyclic compounds.[12] In most of the cases, a tertiary amine has been used as one of the partners whereas α-C–H bond has been activated. In 2010, Maiti and co-workers reported cross-dehydrogenative sp^3 C–O bond formation an iminium ion from amide to construct dihydro-oxazinone derivatives,[13a] and also recently Maiti's group reported copper-catalyzed C(sp^3)–H functionalization/cyclization of 2-amino-*N*,*N*-dialkylbenzamides for the synthesis of 2,3-disubstituted 4(3*H*)-quinazolinone derivatives.[13b] Application of this strategy in intramolecular C–heteroatom bond



Scheme 1 Our present strategy for the synthesis of quinazolinone derivatives

formation to synthesize challenging heterocycles and pharmaceutically important compounds is less studied. Newly established methodology leading to the natural products is in high demand for modern organic synthesis.[14]

In this context, we are pleased to report intramolecular cross-dehydrogenative coupling for C–N bond formation under aerobic conditions for the synthesis of quinazolin-4(3*H*)-ones from isatoic anhydride and amines (benzylic and aliphatic) with copper(I) catalyst via ring-opening cyclization (ROC) strategy (Scheme 1). During this process an iminium ion intermediate is formed, which is subsequently trapped by an amine nucleophile.

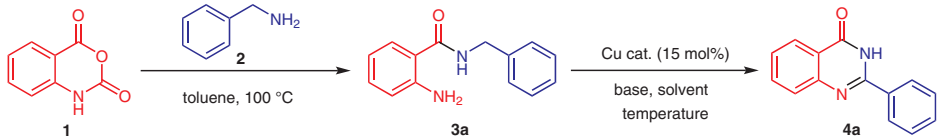
Rutaecarpine, as a kind of natural quinazolinecarboline alkaloid was isolated from fruits of *Evodia rutaecarpa*, a plant used for treatment of headache, cholera, and dysentery in Chinese medicine. Due to the medicinal importance of this alkaloid, various synthetic routes have been developed.[1a,15] Recently Jieping Zhu et al. synthesized rutaecarpine and (±)-evodiamine by a silver salt-catalyzed insertion of the isocyano group into the N–H bond of the tryptamine followed by in situ lactamization.[16] Herein, we describe a shorter route to rutaecarpine from isatoic anhydride and tryptoline via ROC strategy.

Initially, we embarked on our study by examining the reaction of 2-amino-*N*-benzylbenzamide (**3a**) in the presence of K_2CO_3 as the base and $Cu(OAc)_2$ as the catalyst at 90 °C in DMSO, which afforded 2-phenylquinazolin-4(3*H*)-one (**4a**) in 45% yield (Table 1, entry 1).

Further screening of various copper(II) and copper(I) catalyst could promote the reaction and CuBr was found to be the optimal choice (Table 1, entries 1–6). To improve the yield of the product different bases were screened with CuBr and DMSO as solvent furnishing the product in 25–68% yields at 90 °C (entries 7–9). Then, different solvents such as DMF, MeCN, toluene, DCE, and MeOH were investigated, which afforded **4a** in lower yields (entries 10–14). Among the solvents examined, DMSO exhibited the best transformation on giving the product **4a** in 68% yield (entry 8). Upon conducting the reaction under argon instead of oxygen, the reaction proceeded in 6 hours and the yield decreased to 62%. Also the reaction under open air proceeded in 3 hours and provided 64% yield (entry 15, 16). Next, the reaction temperature was varied at 80 °C, 100 °C, and 120 °C, resulting in the isolation of the product **4a** in 70% yield at 100 °C (entries 17–19). When the reaction was run in the absence of CuBr, it afforded **4a** in a diminished yield, while in the absence of KOtBu no reaction product was formed. Thus, these experiments indicate that copper and base are pivotal for the reaction (entries 20, 21).

With the optimized reaction conditions in hand, the scope of the reaction was investigated by varying both the benzylamines and the isatoic anhydride as shown in Scheme 2. The electronic effect of 2-amino-*N*-benzylben-

Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]
1	$Cu(OAc)_2$	K_2CO_3	DMSO	90	45
2	$CuBr_2$	K_2CO_3	DMSO	90	49
3	CuI	K_2CO_3	DMSO	90	52
4	CuBr	K_2CO_3	DMSO	90	55
5	Cu_2O	K_2CO_3	DMSO	90	50
6	CuBr	K_2CO_3	DMSO	90	58
7	CuBr	NaOtBu	DMSO	90	62
8	CuBr	KO*t*Bu	DMSO	90	68
9	CuBr	NEt_3	DMSO	90	25
10	CuBr	KO*t*Bu	DMF	90	62
11	CuBr	KO*t*Bu	MeCN	90	60
12	CuBr	KO*t*Bu	Toluene	90	n.d.
13	CuBr	KO*t*Bu	DCE	90	n.d.
14	CuBr	KO*t*Bu	MeOH	90	n.d.
15	CuBr	KO*t*Bu	DMSO	90	62[c]
16	CuBr	KO*t*Bu	DMSO	90	64[d]
17	CuBr	KO*t*Bu	DMSO	80	61
18	**CuBr**	KO*t*Bu	**DMSO**	**100**	**70**
19	CuBr	KO*t*Bu	DMSO	120	60
20	–	KO*t*Bu	DMSO	100	10
21	CuBr	–	DMSO	100	0

[a] Reaction conditions: **3a** (0.22 mmol), base (0.44 mmol), and solvent (1 mL) under O_2 for 2 h.
[b] Isolated yields after column chromatography. n.d. = Not detected.
[c] Reaction was performed under argon, 6 h.
[d] Reaction under open air, 3 h.

zamides exerted no obvious influence upon the reaction. For example, the electron-rich 2-amino-*N*-benzylbenzamides showed good reactivity to afford the corresponding quinazolin-4(3*H*)-ones **4a–d** in 62–70% yields. At the same time, the 2-amino-*N*-benzylbenzamides with electron-withdrawing substituents, including F and Cl participated in the reaction smoothly affording the products **4e–g** in 56–60% yields. The relative sinking product formation observed for different substituted 2-amino-5-chloro-N-benzylbenzamide deactivates (**3h–3m**), is due to the deactivation of the amine nucleophilicity, thereby considerably decreasing the efficiency of the cyclization reaction (**4h–4m**, 45-62%). The structure of the **4b** was confirmed by X-ray crystal structure analysis (Figure 2).

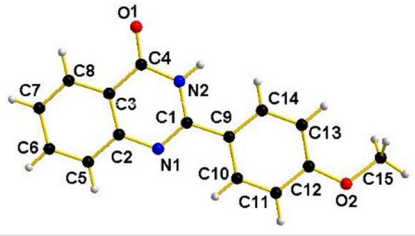
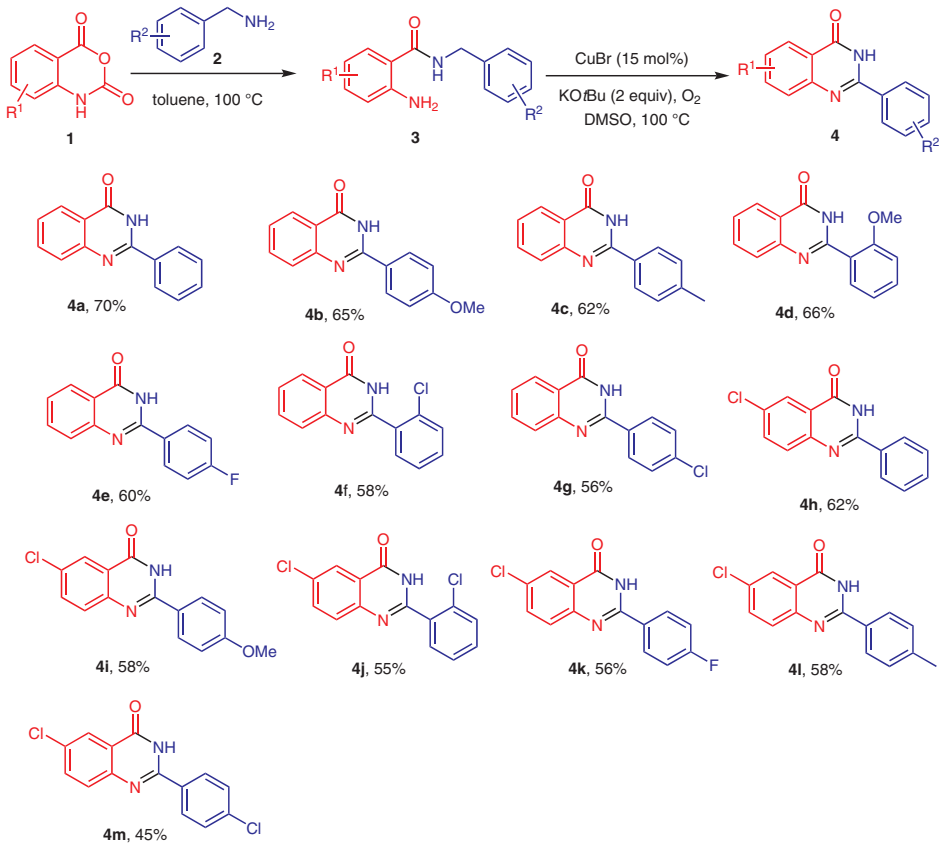


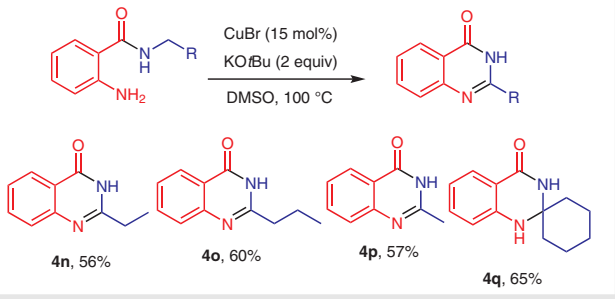
Figure 2 X-ray crystal structure of product **4b**. Thermal ellipsoids are drawn at 30% probability level.[17] For details, see the Supporting Information.

To our delight, 2-amino-*N*-alkylbenzamide derivatives synthesized from aliphatic primary amines such as *n*-propyl and *n*-butyl also underwent intramolecular α-C–H amination giving the products **4n** and **4o** in good yields. In contrast, isopropylamine provided the unexpected product 2-methylquinazolin-4(3*H*)-one (**4p**) by C–C bond cleavage.[18] Differently, cyclohexylamine afforded the 1′*H*-spiro[cyclo-



Scheme 2 Scope of isatoic anhydrides and benzylamines. *Reagents and conditions*: **3** (0.22 mmol), CuBr (15 mol%), KO*t*Bu (2 equiv), DMSO (1 mL), O_2, 100 °C.

hexane-1,2′-quinazolin]-4′(3′*H*)-one (**4q**) in good yield under the standard reaction conditions (Scheme 3, **4n–q**, 56–65%).

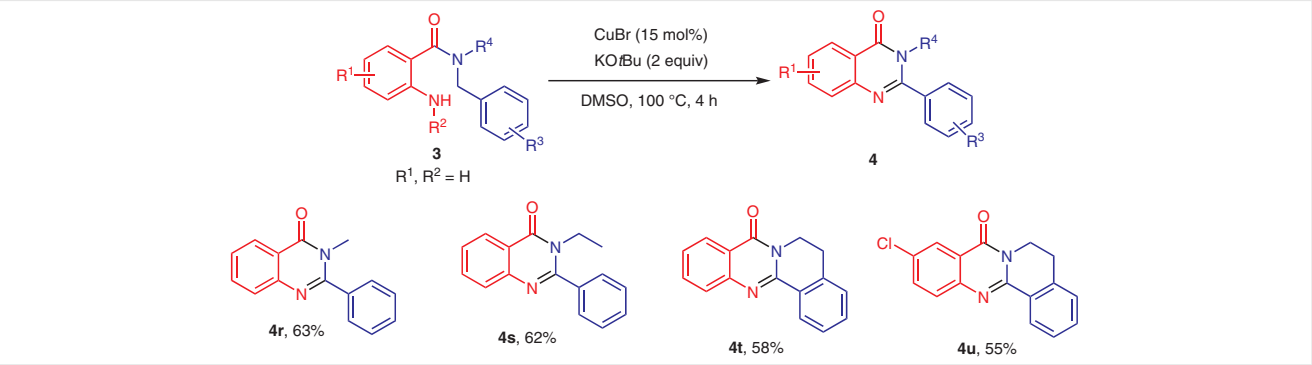


Scheme 3 Scope of isatoic anhydrides and aliphatic amines

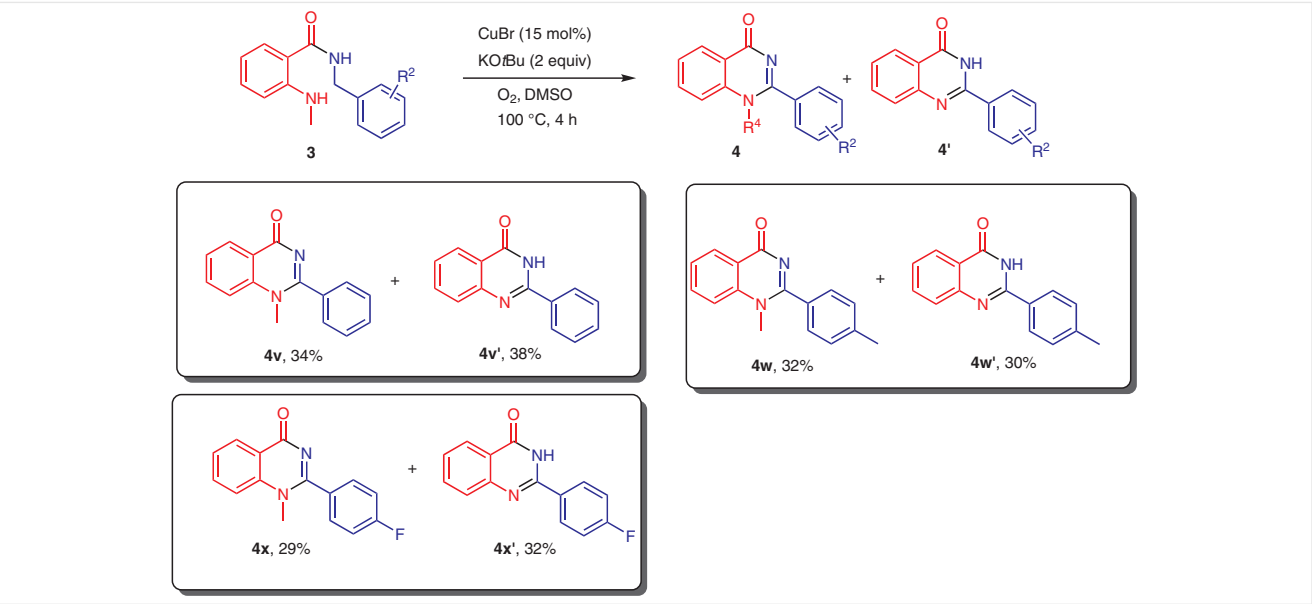
After the successful synthesis of quinazolin-4(3*H*)-ones from isatoic anhydride and primary amines (benzyl and aliphatic), attempts to examine the site selectivity aspect of the ROC strategy were conducted using a number of unsymmetrical amides **3**, which were synthesized from isatoic anhydride and unsymmetrical secondary amines (Scheme 4). In spite of having two possible *N*-methylene sites for cross dehydrogenative coupling, C–N bond formation in **4r** and **4s** selectively undergoes cyclization only at the benzylic position in the presence of an *N*-methyl or *N*-ethyl moiety. And also, complete selectivity for C–N bond formation was observed at the benzylic side of tetrahydroisoquinoline while incorporated the 2-aminobenzamide (**4t**) and 2-amino-5-chlorobenzamide (**4u**) (Scheme 4).

After having successful development of copper-catalyzed intramolecular cyclization for the synthesis of quinazolin-4(3*H*)-ones **4** from 2-amino-*N*-alkylbenzamide derivatives **3**, subsequently, we tested the *N*-methylisatoic anhydride ring-opened benzylamine product **3** to provide the 2-arylquinazolinones by N–C bond cleavage along with the 1-methyl-2-phenylquinazolin-4(1*H*)-one derivatives (Scheme 5, 4v–x).

Compared to C–H bond cleavage, N–C bond cleavage has received much attention in organic chemistry, due to the inertness of this bond.[19] To further rule out the demethylation, we performed a reaction in different solvents DMF and MeCN, which provided demethylation product along with expected product. On the basis of these experimental results, we propose a reasonable mechanistic pathway. We have demonstrated a copper-catalyzed approach for the



Scheme 4 Scope of isatoic anhydride and unsymmetric benzylamines



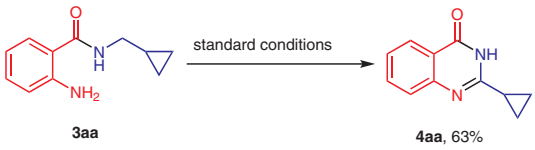
Scheme 5 Substrate scope for the CuBr-catalyzed synthesis of quinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones

synthesis of 2-substituted quinazolinones through an intramolecular N–C bond cleavage with air as the oxidant under basic conditions.

To probe the mechanism of intramolecular α-C–H amination, preliminary control experiments were conducted whether the reaction proceeds through a radical pathway. We performed the standard reaction in the presence of radical scavengers like 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), di-*tert*-butyl peroxide (DTP) and *tert*-butyl peroxybenzoate (TBPB) (Scheme 6), which showed no significant decrease in the yield of the product **4a**, and also did not observe any radical trapped intermediates. To further rule out the radical pathway, we performed a radical clock experiment on the cyclopropyl-substituted derivative **3aa** under standard conditions, which provided 2-cyclopropylquinazolin-4(3*H*)-one (**4aa**) without formation of any ring-opened coupling products (Scheme 7).

Radical scavengers	Yield
TEMPO (2 equiv)	68%
DTP (2 equiv)	66%
TBPB (2 equiv)	68%

Scheme 6 Control experiments

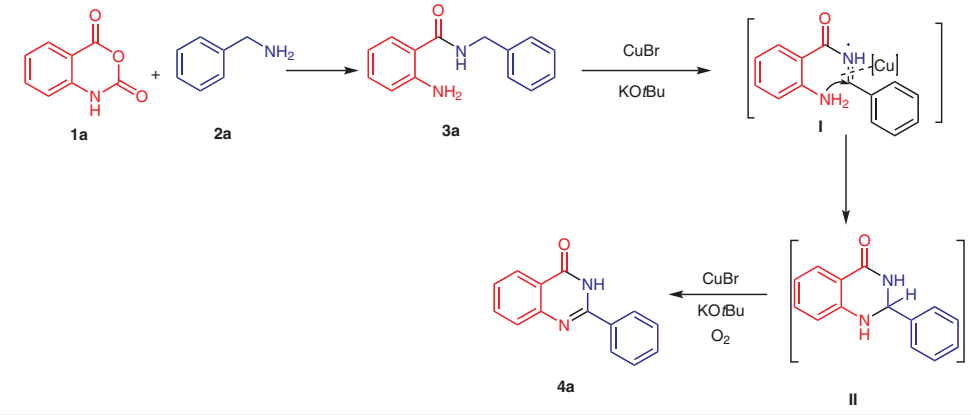


Scheme 7 Radical clock experiment

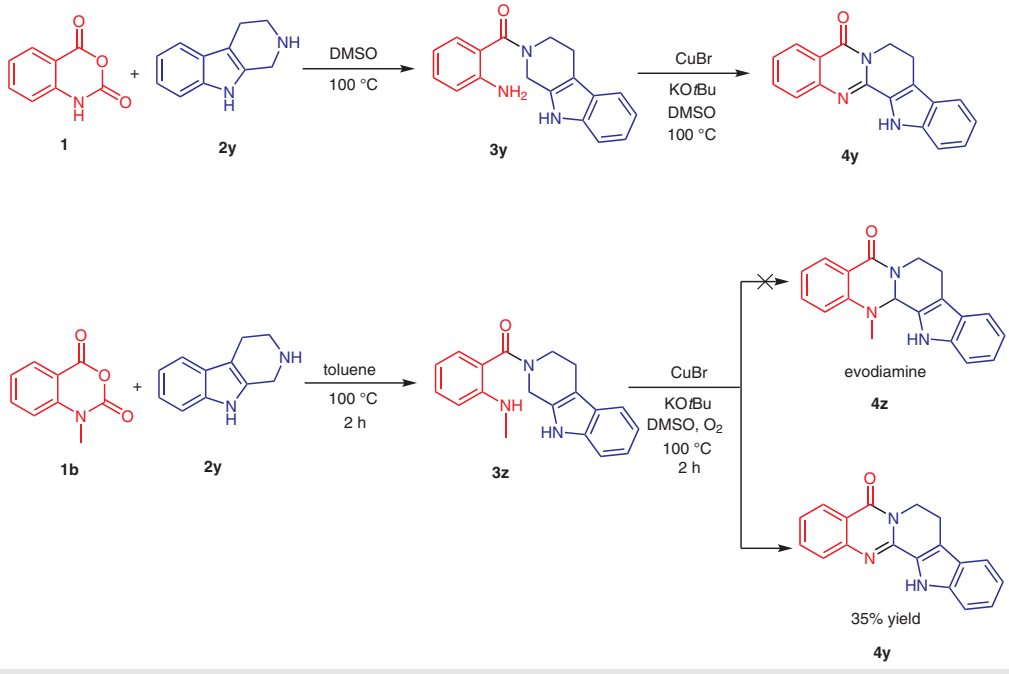
On the basis of above results, a tentative ionic reaction mechanism is proposed as shown in Scheme 8. During the course of these reactions, an iminium ion is found as the key intermediate **I** in this transformation, subsequently the iminium ion undergoes intramolecular cyclization followed by oxidation, to furnish the desired product **4a** (Scheme 8).

Having developed a copper-catalyzed rapid synthesis of 2-substituted quinazolin-4(3*H*)-ones, this ROC strategy was applied for the synthesis of our target natural product rutaecarpine. Thus, isatoic anhydride (**1**) was treated with tryptoline (**2y**) in DMSO for 2 hours to give the desired product **3y**. The compound **3y** on treatment with CuBr and KO*t*Bu under oxygen at 100 °C afforded rutaecarpine (**4y**) in 60% yield. This strategy was also applied for the synthesis of evodiamine but we failed to get the expected product **4z**. On treatment of **3z** with CuBr and KO*t*Bu under oxygen rutaecarpine (**4y**) was obtained in 35% yield (Scheme 9).

In summary, we have developed a copper-catalyzed intramolecular α-C–H amination of C(sp^3)–H bond for the synthesis of quinazolin-4(3*H*)-one derivatives from com-



Scheme 8 Plausible reaction mechanism for the synthesis of quinazolin-4(3*H*)-ones **4**



Scheme 9 Synthesis of rutaecarpine

mercially available isatoic anhydride and primary and secondary amines. This protocol shows good functional group tolerance and allows access to a range of 2-alkyl- and spiroquinazolin-4(1*H*)-one derivatives in the progress of ROC strategy. It is the first general method to construct the potentially useful 2-methylquinazolin-4(3*H*)-one by copper-catalyzed intramolecular C–H amination. The synthetic utility of this strategy was illustrated by the convenient synthesis of rutaecarpine via ROC strategy.

IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard TMS (δ_H = 0.00) or $CHCl_3$ (δ_H = 7.25). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer at r.t. in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 (central line of triplet)]. In the ^{1}H NMR, standard abbreviations were used to denote the multiplicity. The assignments of signals were confirmed by ^{1}H and ^{13}C spectra. High-resolution mass spectra (HRMS) were recorded using Q-TOF multimode source. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. 2-Amino-*N*-benzylbenzamides **3** were prepared by using known procedures. MeOH and toluene were dried over sodium metal and DMSO, MeCN and DCE were dried over CaH_2.

All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of PE and EtOAc as eluents. Reactions were generally run under an O_2 atmosphere. Solvents were distilled prior to use; PE with a boiling range of 40–60 °C was used.

2-Amino-*N*-benzylbenzamides; 2-Amino-*N*-benzylbenzamide (3a); Typical Procedure 1

Isatoic anhydride (**1a**; 815 mg, 5 mmol) in toluene was treated with benzylamine (**2a**; 547 mg, 5 mmol) at 100 °C for 1–2 h and monitored by TLC. After completion of the reaction, the mixture was washed with H_2O and extracted with EtOAc. The organic layer was dried (anhydrous Na_2SO_4), concentrated in vacuum under reduced pressure, and then purified by silica gel column chromatography using EtOAc and hexane (15:85) as eluent to afford the corresponding product **3a** as a white solid; yield: 1.1 g (98%).[19]

2-Phenylquinazolin-4(3*H*)-ones Through ROC Strategy; General Procedure 2

To a mixture of the respective 2-amino-*N*-benzylbenzamide **3** (0.2 mmol), CuBr (15 mol%), and KO*t*Bu (0.44 mmol) in a 10 mL Schlenk tube was added of DMSO (2 mL), and the mixture was stirred at 100 °C for 2–4 h (monitored by TLC) under an O_2 balloon. After the completion of the reaction, the reaction mixture was cooled and was quenched with ice-cold H_2O and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine and dried (anhydrous Na_2SO_4). The crude extract was purified by filtration through a silica gel (100–200 mesh) column using hexane and EtOAc (8:2) as eluent to yield the desired quinazolinone product **4**.

2-Phenylquinazolin-4(3*H*)-ones through ROC Strategy in Sequential One-Pot Reaction; General Procedure 3

To a mixture of isatoic anhydride **1** (0.25 mmol) and benzylamine **2** (0.25 mmol) in a 10 mL Schlenk tube was added DMSO (2 mL), and the mixture was stirred at 100 °C for 1–2 h and monitored by TLC. To this reaction mixture was added CuBr (15 mol%) and KO*t*Bu (2 equiv), and the mixture was stirred at 100 °C for 2–3 h (monitored by TLC) under an O_2 balloon. After the completion of the reaction, the mixture was cooled, quenched with ice-cold H_2O, and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine and dried (anhydrous Na_2SO_4). The crude extract was purified by filtration through a silica gel (100–200 mesh) column using EtOAc and hexane (8:2) as eluent to yield the desired quinazolinone product **4**.

2-Phenylquinazolin-4(3*H*)-one (4a)

White solid; yield: 34 mg (70%); mp 140 ° C.

IR (MIR-ATR): 3396, 1655, 1554, 1469, 995, 823, 762, 682, 616 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.51 (m, 4 H), 7.84–7.81 (m, 2 H), 8.35–8.27 (m, 3 H), 11.81 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.98, 151.81, 149.54, 134.93, 132.83, 131.67, 129.05, 128.02, 127.46, 126.81, 126.38, 120.84.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_{10}N_2O$ [M + H$^+$]: 223.0866; found: 223.0862.

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (4b)

White solid; yield: 36 mg (65%); mp 232 °C.

IR (MIR-ATR): 1679, 1600, 1523, 1479, 1247, 1177, 1030, 834, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 3.8 (s, 3 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 7.35 (td, *J* = 7.3, 7.3 Hz, 1 H), 7.69–7.63 (m, 2 H), 8.14–8.10 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 162.16, 161.02, 151.08, 148.35, 133.25, 128.41, 126.39, 124.19, 119.90, 112.92, 54.36.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{12}N_2O_2$ [M + H$^+$]: 253.0972; found: 253.0972.

2-(*p*-Tolyl)quinazolin-4(3*H*)-one (4c)

White solid; yield: 32 mg (62%); mp 262 °C.

IR (MIR-ATR): 3741, 1669, 1608, 1550, 1299, 941, 832, 767, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.75 (br s, 1 H), 8.33 (d, *J* = 7.8 Hz, 1 H), 8.16 (d, *J* = 7.3 Hz, 2 H), 7.81–7.79 (m, 2 H), 7.49 (t, *J* = 7.1, 7.1 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 2 H), 2.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.00, 151.86, 149.64, 142.18, 134.84, 129.98, 129.75, 127.9, 127.38, 126.56, 126.36, 120.78, 21.56.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{12}N_2O$ [M + H$^+$]: 237.1022; found: 237.1024.

2-(2-Methoxyphenyl)quinazolin-4(3*H*)-one (4d)

White solid; yield: 37 mg (66%); mp 170 °C.

IR (MIR-ATR): 3743, 1676, 1593, 1557, 1474, 1233, 1013, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.95 (br s, 1 H), 8.51 (dd, *J* = 7.83, 1.96 Hz, 1 H), 8.19–8.36 (m, 1 H), 7.63–7.83 (m, 2 H), 7.38–7.53 (m, 2 H), 7.11–7.18 (m, 1 H), 7.04 (d, *J* = 8.31 Hz, 1 H), 4.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.89, 157.76, 150.77, 149.39, 134.45, 133.17, 131.51, 127.85, 126.45, 126.39, 121.83, 121.18, 119.91, 111.81, 56.14.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{12}N_2O_2$ [M + H$^+$]: 253.0972; found: 253.0971.

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (4e)

White solid; yield: 32 mg (60%); mp 260 °C.

IR (MIR-ATR): 3742, 1659, 1620, 1215, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 12.09 (br s, 1 H), 8.17 (dd, *J* = 8.1, 6.1 Hz, 2 H), 7.69–7.67 (m, 2 H), 7.39–7.34 (m, 2 H), 7.14–7.10 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 163.31, 151.39, 149.13, 134.39, 130.03, 129.94, 127.60, 126.06, 121.02, 115.78, 115.56.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_9FN_2O$ [M + H$^+$]: 241.0772; found: 241.0777.

2-(2-Chlorophenyl)quinazolin-4(3*H*)-one (4f)

White solid; yield: 33 mg (58%); mp 155 °C.

IR (MIR-ATR): 3743, 1666, 1605, 1559, 1512, 1474, 1334, 1292, 768, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.87 (br s, 1 H), 8.35–8.29 (m, 1 H), 8.28–8.27 (m, 2 H), 7.85–7.81 (m, 2 H), 7.61–7.59 (m, 2 H), 7.53–7.49 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.99, 151.79, 149.55, 134.92, 132.83, 131.66, 129.05, 128.02, 127.46, 126.80, 126.37, 120.85.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_9ClN_2O$ [M + H$^+$]: 257.0476; found: 257.0480.

2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (4g)

White solid; yield: 32 mg (56%); mp 200 °C.

IR (MIR-ATR): 3742, 1740, 1703, 1641, 1516, 1462, 1515, 1240, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 12.49 (br s, 1 H), 8.25–8.18 (m, 3 H), 7.77–7.73 (m, 2 H), 7.53–7.48 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 167.6, 156.3, 153.8, 141.8, 139.3, 136.6, 134.5, 133.6, 133.5, 132.6, 131.5, 130.9, 126.2.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_9ClN_2O$ [M + H$^+$]: 257.0476; found: 257.0476.

6-Chloro-2-phenylquinazolin-4(3*H*)-one (4h)

White solid; yield: 35 mg (62%); mp 230 °C.

IR (MIR-ATR): 3742, 2923, 1680, 1646, 1509, 1467, 1250, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 8.21–8.18 (m, 2 H), 7.74–7.68 (m, 2 H), 7.55 (br s, 1 H), 7.36 (d, *J* = 5.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 152.44, 147.35, 134.13, 132.33, 131.17, 131.03, 129.06, 128.44, 128.21, 127.41, 124.91, 121.93.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_9ClN_2O$ [M + H$^+$]: 257.0476, found: 257.0476.

6-Chloro-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (4i)

White solid; yield: 37 mg (58%); mp 145 °C.

IR (MIR-ATR): 3723, 1666, 1603, 1508, 1253, 1177, 1031, 832 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 11.72 (br s, 1 H), 8.28–8.17 (m, 2 H), 7.76–7.68 (m, 2 H), 7.39 (s, 1 H), 7.03 (dd, *J* = 8.8, 2.4 Hz, 2 H), 3.89 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 163.36, 149.49, 134.66, 134.37, 129.32, 129.20, 127.51, 126.11, 126.01, 125.47, 120.86, 114.10, 55.39.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{11}ClN_2O_2$ [M + H$^+$]: 287.0582; found: 257.0585.

6-Chloro-2-(2-chlorophenyl)quinazolin-4(3*H*)-one (4j)

White solid; yield: 35 mg (55%); mp 270 °C.

IR (MIR-ATR): 3394, 1678, 995, 824, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 8.14–8.12 (m, 2 H), 7.81 (s, 1 H), 7.65–7.48 (m, 2 H), 7.45–7.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 160.57, 151.46, 146.38, 133.15, 131.37, 130.07, 128.17, 127.23, 126.52, 123.90, 121.00.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_8Cl_2N_2O$ [M + H$^+$]: 291.0086; found: 291.0076.

6-Chloro-2-(4-fluorophenyl)quinazolin-4(3*H*)-one (4k)

White solid; yield: 34 mg (56%); mp 260 °C.

IR (MIR-ATR): 3419, 1655, 1506, 1420, 1288, 1182, 1023, 994, 825, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 12.64 (br s, 1 H), 8.23 (dd, *J* = 8.6, 5.1 Hz, 2 H), 8.08–8.05 (m, 1 H), 7.74–7.67 (m, 2 H), 7.24 (t, *J* = 8.3, and 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 161.41, 151.55, 147.32, 135.81, 134.34, 130.94, 130.1, 129.31, 128.72, 124.83, 115.45, 115.24.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_8ClFN_2O$ [M + H$^+$]: 275.0382; found: 275.0382.

6-Chloro-2-(*p*-tolyl)quinazolin-4(3*H*)-one (4l)

White solid; yield: 37 mg (58%); mp 230 °C.

IR (MIR-ATR): 2920, 1667, 1600, 1466, 1286, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 12.46 (br s, 1 H), 8.20–8.09 (m, 2 H), 7.9 (d, *J* = 3.4 Hz, 1 H), 7.76–7.73 (m, 2 H), 731 (d, *J* = 6.8, 2 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.39, 140.22, 132.97, 129.62, 128.38, 127.76, 126.31, 123.68, 120.75, 19.85.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{11}ClN_2O$ [M + H$^+$]: 271.0633; found: 271.0636.

6-Chloro-2-(4-chlorophenyl)quinazolin-4(3*H*)-one (4m)

White solid; yield: 28 mg (45%); mp 320 °C.

IR (MIR-ATR): 3391, 1659, 1021, 997, 825, 763, 624 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.77 (br s, 1 H), 8.31–8.13 (m, 2 H), 8.09 (s, 1 H), 7.95–7.82 (m, 1 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.68–7.54 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.20, 142.93, 136.49, 134.75, 131.26, 130.95, 129.67, 128.70, 128.62, 128.27, 127.81, 124.86.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_8Cl_2N_2O$ [M + H$^+$]: 291.0086; found: 271.0089.

2-Ethylquinazolin-4(3*H*)-one (4n)

White solid; yield: 22 mg (56%); mp 210 °C.

IR (MIR-ATR): 3841, 1682, 1586, 1420, 1234, 1181, 774, 756, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.23 (br s, 1 H), 8.30 (dd, *J* = 8.07, 1.22 Hz, 1 H), 7.60–7.86 (m, 2 H), 7.33–7.60 (m, 1 H), 2.86 (q, *J* = 7.34 Hz, 2 H), 1.47 (t, *J* = 7.58 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.57, 157.79, 149.53, 134.81, 127.22, 126.36, 126.24, 120.50, 29.17, 11.60.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{10}H_{10}N_2O$ [M + H$^+$]: 175.0866; found: 175.0865.

2-Propylquinazolin-4(3*H*)-one (4o)

White solid; yield: 25 mg (60%); mp 180 °C.

IR (MIR-ATR): 3641, 1686, 1556, 1410, 1209, 1191, 776, 766, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.24 (br s, 1 H), 8.30 (dd, *J* = 8.07, 1.22 Hz, 1 H), 7.59–7.87 (m, 2 H), 7.39–7.56 (m, 1 H), 2.66–2.88 (m, 2 H), 1.94 (dq, *J* = 15.10, 7.52 Hz, 2 H), 1.09 (t, *J* = 7.34 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.53, 156.89, 149.53, 134.79, 127.22, 126.21, 120.48, 37.74, 21.05, 13.77.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{12}N_2O$ [M + H$^+$]: 189.1022; found: 189.1022.

2-Methylquinazolin-4(3*H*)-one (4p)

White solid; yield: 20 mg (57%); mp 280 °C.

IR (MIR-ATR): 3346, 1586, 1456, 1310, 1109, 991, 778, 798, 688 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.21 (br s, 1 H), 7.99–8.16 (m, 1 H), 7.72–7.85 (m, 1 H), 7.48–7.60 (m, 1 H), 7.44 (t, *J* = 7.58 Hz, 1 H), 3.42 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.71, 154.24, 145.36, 134.27, 126.7, 125.8, 125.63, 120.56, 21.39.

HRMS (ESI$^+$): *m*/*z* calcd for $C_9H_8N_2O$ [M + H$^+$]: 161.0709; found: 161.0709.

1′*H*-Spiro[cyclohexane-1,2′-quinazolin]-4′(3′*H*)-one (4q)

White solid; yield: 31 mg (65%); mp 140 °C.

IR (MIR-ATR): 3324, 3040, 1679, 1580, 1486, 1392, 1182, 1120, 982, 776, 723, 685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.29 (br s, 1 H), 8.28 (dd, *J* = 1.2, 8.1 Hz, 1 H), 7.86–7.60 (m, 2 H), 7.58–7.36 (m, 1 H), 2.83–2.71 (m, 2 H), 2.28–2.10 (m, 1 H), 2.10–1.93 (m, 1 H), 1.91–1.78 (m, 3 H), 1.01–0.84 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.86, 156.74, 134.81, 127.22, 126.40, 126.26, 36.01, 31.38, 27.22, 22.35, 13.94.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{13}H_{16}N_2O$ [M + H$^+$]: 217.1335; found: 217.1328.

3-Methyl-2-phenylquinazolin-4(3*H*)-one (4r)

White solid; yield: 33 mg (63%); mp 132 °C.

IR (MIR-ATR): 1673, 1562, 1472, 1352, 1023, 773, 641 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.31 Hz, 1 H), 7.71–7.81 (m, 2 H), 7.45–7.61 (m, 6 H), 3.50 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.73, 156.14, 147.33, 135.42, 134.32, 130.08, 128.90, 127.51, 127.01, 126.69, 120.54, 34.28.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{12}N_2O$ [M + H$^+$]: 237.1022; found: 237.1030.

3-Ethyl-2-phenylquinazolin-4(3*H*)-one (4s)

White solid; yield: 34 mg (62%); mp 125 °C.

IR (MIR-ATR): 1673, 1564, 1468, 1378, 1254, 1066, 772, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 7.34 Hz, 1 H), 7.64–7.94 (m, 2 H), 7.37–7.63 (m, 6 H), 4.04 (d, *J* = 6.85 Hz, 2 H), 1.22 (t, *J* = 7.09 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16 2.01, 156.20, 147.21, 135.62, 134.29, 129.79, 128.82, 127.67, 127.46, 126.95, 126.71, 121.00, 41.19, 14.12.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{14}N_2O$ [M + H$^+$]: 251.1179; found: 251.1185.

5*H*-Isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (4t)

White solid; yield: 32 mg (58%); mp 140 °C.

IR (MIR-ATR): 1670, 1558, 1475, 1394, 1335, 1150, 768, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (dd, *J* = 7.82, 1.47 Hz, 1 H), 8.27–8.39 (m, 1 H), 7.70–7.84 (m, 2 H), 7.38–7.57 (m, 3 H), 7.22–7.34 (m, 1 H), 4.33–4.48 (m, 2 H), 3.11 (t, *J* = 6.60 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.74, 149.40, 147.84, 137.07, 134.23, 131.73, 129.6, 128.05, 127.65, 127.63, 127.51, 126.88, 126.54, 120.78, 39.63, 27.49.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{12}N_2O$ [M + H$^+$]: 249.1022; found: 249.1028.

10-Chloro-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one (4u)

White solid; yield: 34 mg (55%); mp 172 °C.

IR (MIR-ATR): 1672, 1555, 1466, 1394, 1335, 1240, 1153, 1067, 895, 833, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 7.34 Hz, 1 H), 8.27 (d, *J* = 1.96 Hz, 1 H), 7.61–7.81 (m, 2 H), 7.39–7.56 (m, 2 H), 7.19–7.35 (m, 1 H), 4.32–4.52 (m, 2 H), 3.11 (t, *J* = 6.60 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.75, 149.63, 146.33, 137.03, 134.70, 132.21, 131.98, 129.27, 128.05, 127.72, 127.59, 126.22, 121.70, 39.77, 27.36.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{11}ClN_2O$ [M + H$^+$]: 283.0633; found: 283.0633.

1-Methyl-2-phenylquinazolin-4(1*H*)-one (4v)

Brown solid; yield: 18 mg (34%); mp 210 °C.

IR (MIR-ATR): 1640, 1602, 1519, 1458, 1393, 1257, 1144, 1071, 1036, 765, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (dd, *J* = 7.82, 1.47 Hz, 1 H), 7.73–7.88 (m, 1 H), 7.59–7.69 (m, 2 H), 7.44–7.59 (m, 5 H), 3.73 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.79, 162.49, 141.82, 134.76, 133.94, 130.73, 128.88, 128.74, 128.65, 126.27, 120.41, 115.20, 37.98.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{12}N_2O$ [M + H$^+$]: 237.1022; found: 237.1027.

2-Phenylquinazolin-4(3*H*)-one (4v′)

White solid; yield: 19 mg (38%); mp 142 °C.

IR (MIR-ATR): 3396, 1655, 1554, 1469, 995, 823, 762, 682, 616 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.56 (br s, 1 H), 8.10–8.25 (m, 3 H), 7.80–7.89 (m, 1 H), 7.70–7.80 (m, 1 H), 7.37–7.62 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.21, 152.26, 148.70, 134.57, 132.67, 131.36, 128.57, 127.73, 127.47, 126.55, 125.82, 120.94.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_{10}N_2O$ [M + H$^+$]: 223.0866, found: 223.0862.

1-Methyl-2-(*p*-tolyl)quinazolin-4(1*H*)-one (4w)

Yellow solid; yield: 18 mg (32%); mp 165 °C.

IR (MIR-ATR): 1688, 1619, 1514, 1464, 1418, 1286, 1041, 967, 785, 674 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 7.82 Hz, 1 H), 7.66–7.85 (m, 1 H), 7.43–7.60 (m, 5 H), 7.21–7.36 (m, 2 H), 3.73 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.87, 162.60, 141.93, 141.15, 133.81, 131.85, 129.22, 129.03, 128.59, 126.08, 120.36, 115.24, 38.12, 21.50.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{14}N_2O$ [M + H$^+$]: 251.1179; found: 251.1178.

2-(*p*-Tolyl)quinazolin-4(3*H*)-one (4w′)

White solid; yield: 16 mg (30%); mp 150 °C.

IR (MIR-ATR): 3742, 1672, 1605, 1556, 1473, 1294, 767, 686 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.68 (br s, 1 H), 8.22–8.43 (m, 1 H), 8.16 (m, *J* = 8.31 Hz, 2 H), 7.76–7.85 (m, 2 H), 7.49 (ddd, *J* = 7.95, 6.24, 1.96 Hz, 1 H), 7.37 (m, *J* = 7.83 Hz, 2 H), 2.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.96, 151.83, 149.66, 142.18, 134.83, 130.00, 129.75, 128.07, 127.91, 127.36, 126.55, 126.37, 120.79, 21.55.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{12}N_2O$ [M + H$^+$]: 237.1022; found: 237.1026.

2-(4-Fluorophenyl)-1-methylquinazolin-4(1*H*)-one (4x)

White solid; yield: 16 mg (29%); mp 210 °C.

IR (MIR-ATR): 1640, 1493, 1455, 1394, 1225, 1147, 856, 766, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (dd, *J* = 7.82, 1.47 Hz, 1 H), 7.76 (ddd, *J* = 8.44, 7.21, 1.47 Hz, 1 H), 7.61–7.69 (m, 2 H), 7.42–7.53 (m, 2 H), 7.12–7.21 (m, 2 H), 3.72 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.65, 165.28, 161.47, 141.79, 133.97, 131.35, 131.27, 130.85, 128.59, 126.32, 120.33, 115.95, 115.73, 115.29, 38.08.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{11}FN_2O$ [M + H$^+$]: 255.0928; found: 255.0921.

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (4x′)

White solid; yield: 17 mg (32%); mp 260 °C.

IR (MIR-ATR): 3742, 1659, 1620, 1215, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ = 12.09 (br s, 1 H), 8.17 (dd, *J* = 8.1, 6.1 Hz, 2 H), 7.69–7.67 (m, 2 H), 7.39–7.34 (m, 2 H), 7.14–7.10 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 163.31, 151.39, 149.13, 134.39, 130.03, 129.94, 127.60, 126.06, 121.02, 115.78, 115.56.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_9FN_2O$ [M + H$^+$]: 241.0772; found: 241.0777.

2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indole (2y)

Brown solid; yield: 27 mg (72%); mp 152 °C.

IR (MIR-ATR): 3743, 3648, 1731, 1642, 1515, 1462, 1287, 801, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (br s, 1 H), 7.48 (d, *J* = 7.34 Hz, 1 H), 7.20–7.38 (m, 1 H), 7.04–7.18 (m, 2 H), 4.00 (s, 2 H), 3.17 (t, *J* = 5.62 Hz, 2 H), 2.75 (t, *J* = 5.38 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.66, 132.74, 127.57, 121.47, 119.37, 117.86, 110.70, 108.66, 43.86, 43.16, 22.45.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{12}N_2$ [M + H$^+$]: 173.1073; found: 173.1073.

7,8-Dihydroindolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-5(13*H*)-one (4y; Rutaecarpine)

White solid; yield: 38 mg (60%); mp 136 °C.

IR (MIR-ATR): 1613, 1590, 1469, 1435, 1307, 1234, 1159, 736, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.95 (br s, 1 H), 8.33 (dd, *J* = 8.07, 1.22 Hz, 1 H), 7.54–7.83 (m, 3 H), 7.41 (ddd, *J* = 8.19, 6.72, 1.71 Hz, 1 H), 7.26 (dd, *J* = 5.14, 1.71 Hz, 2 H), 7.15 (ddd, *J* = 8.07, 4.65, 3.42 Hz, 1 H), 4.51–4.68 (m, 2 H), 3.22 (t, *J* = 6.85 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.63, 147.41, 145.20, 138.38, 134.42, 127.29, 127.12, 126.49, 126.26, 125.57, 121.15, 120.59, 120.08, 118.49, 112.16, 41.18, 19.68.

HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{13}N_3O$ [M + H$^+$]: 288.1131; found: 288.1136.

2-Cyclopropylquinazolin-4(3*H*)-one (4aa)

White solid; yield: 26 mg (63%); mp 230 °C.

IR (MIR-ATR): 2922, 2057, 1669, 1604, 1459, 1395, 981, 893, 763, 606 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.66 (br s, 1 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 7.72 (t, *J* = 7.3, 7.3 Hz, 1 H), 7.6 (d, *J* = 8.3 Hz, 1 H), 2.03–1.92 (m, 1 H), 1.36–1.28 (m, 2 H), 1.16–1.1 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.97, 157.96, 149.82, 134.65, 127.01, 126.28, 125.66, 120.5, 34.01, 14.72, 9.62.

Anal. Calcd for $C_{11}H_{10}N_2O$ (186.0793): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.45; H, 5.62; N, 15.48.

Funding Information

We gratefully acknowledge the Council of Scientific and Industrial Research (CSIR 02(0297)/17/EMR-II), New Delhi, India and the Indian Institute of Technology Hyderabad (IITH) for financial support. S.M.P. thanks UGC and S.B. thanks CSIR, New Delhi, India for the award of a research fellowship.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611484.

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